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The therapeutic effects of sevelamer on blood sugar, HbA1c, lipid profile, and hs-CRP in patients with diabetic nephropathy; a preliminary study

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ABSTRACT

Background: Diabetic nephropathy (DN) is one of the major complications of diabetes. Hyperglycemia, inflammation and oxidative stress as well as advanced glycation end products (AGEs) are reported as the risk factors for DN. Sevelamer has shown promising results in reducing inflammation and even HbA1c levels in DN.

Objectives: We aimed to evaluate the therapeutic effects of sevelamer on blood sugar, HbA1c level, lipid profile, and high sensitivity C-reactive protein (hs-CRP) in patients with DN.

Patients and Methods: In this clinical trial, 18 patients (5 males and 13 females with mean age of 61.22 ± 9.32 years) with stages 2-4 of DN were recruited. Patients were administered with 800 mg of sevelamer twice a day for 3 months. Blood sugar, HbA1c, hs-CRP, lipid profile and other laboratory findings were measured before and 1, 2 and 3 months after initiation of the treatment.

Results: There was a significant decline in HbA1c ($P=0.001$), postprandial blood sugar ($P<0.001$) and phosphorus ($P<0.001$) at the end of the study period. Sevelamer had no effect on fasting blood sugar, lipid profile, blood urea nitrogen (BUN), creatinine, Na, K and hs-CRP.

Conclusions: Our results indicated that along with its phosphorus reducing effects, sevelamer plays an important role in decreasing postprandial blood sugar and HbA1c level. Sevelamer had no effects on lipid profile and hs-CRP.

Implication for health policy/practice/research/medical education:

Hyperglycemia, inflammation and oxidative stress as well as advanced glycation end products (AGEs) are reported risk factors of diabetic nephropathy (DN). Besides phosphorus reducing effects, sevelamer could decrease postprandial blood sugar and HbA1c level. Sevelamer had no effects on lipid profile and high sensitivity CRP.

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1. Background

Diabetic nephropathy (DN) is one of the major microvascular complications of diabetes and has become the leading cause of end-stage renal disease (ESRD) (1,2). DN is also a major cause of morbidity and mortality in patients with diabetes due to the progression to ESRD and associated cardiovascular disease (3,4).

Hyperglycemia, inflammation and oxidative stress are reported as the risk factors for the induction and progression of DN (3,4). Along with these factors, advanced glycation end products (AGEs) are another factor which cause the increase of inflammatory markers and oxidative stresses which can result in the progress of chronic kidney disease (CKD) (5). Various studies have

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indicated that enhancing oxidative stress and chronic vascular inflammation exacerbates the prognosis of nephropathy in type II diabetic patients (5-7).

Sevelamer is a non-absorbable calcium and aluminum-free phosphate binder which attaches to phosphorus in the intestine preventing its absorption and causing a decrease in the total phosphorus level (8). It is shown that serum phosphorus is independently correlated with inflammatory parameters (9), and using sevelamer could reduce the inflammation and hs-CRP level by reducing the phosphorus levels (10). A recent study has also indicated that sevelamer has significant effects on hemoglobin A_{1c} (HbA_{1c}) and markers of inflammation in patients with DN (5).

2. Objectives

As there are no related studies in Iran, we aimed to evaluate the therapeutic effects of sevelamer on blood sugar, HbA_{1c}, Lipid profiles, and hs-CRP in patients with DN.

3. Patients and Methods

3.1. Patients

In this clinical trial, we recruited 18 patients with DN visiting nephrology clinics of Imam-Khomeini hospital, Ardabil, Iran. Inclusion criteria were DN stage 2-4, age ≥ 46 years and sugar level of 100-400 mg/dL. Patients with current treatment for hyperphosphatemia, biopsy-proven renal disease other than diabetic kidney disease, hypophosphatemia, hypercalcemia, symptomatic gastrointestinal disorders and concomitant inflammatory diseases were excluded.

3.2. Intervention and biochemical measurement

Patients were assigned to receive sevelamer (800 mg twice a day) for 12 weeks. Patients received all their previous medications and we made no changes in medications or their diets.

HbA_{1c} and lipid profile was measured before and at the end of the study. Other laboratory findings including Ca, P, hs-CRP, fasting and postprandial blood sugar and CBC with differential were measured before and at first, second and third months after the study initiation.

3.3. Ethical issues

The research followed the tenets of the Declaration of Helsinki. The study protocol was approved by the ethics committee of the Ardabil University of Medical Science and all participants gave written informed consent before enrolling in the study. Besides that, the study protocol was registered as In the Iranian Registry of Clinical Trials (identifier: IRCT2016100423559N5; <http://en.search.irct.ir/view/33110>).

3.4. Statistical analysis

All data were analyzed using SPSS20 (version 20; SPSS Inc., Chicago, IL). Results are expressed as mean \pm standard deviation or percentage. Paired samples *t* test and repeated measure of analysis of variance (ANOVA) were used to evaluate the changes in the variables during the study period and *P* values of less than 0.05 were considered statistically significant.

4. Results

The study population comprised of 5 males (27.8%) and 13 females (72.2%) with a mean age of 61.22 ± 9.32 years (range 46-77 years). The mean body mass index was 28.64 ± 1.97 kg/m².

Changes in HbA_{1c} and lipid profile are shown in Table 1. HbA_{1c} was significantly declined following the treatment, but the changes in cholesterol, triglyceride, high-density lipoprotein (HDL-C) and low-density lipoprotein (LDL-C) levels were not significant. Sevelamer had significantly decreased phosphorus levels (Table 2). There was also a significant decrease in postprandial blood sugar, while it did not affect fasting blood sugar. Also, there were no changes in blood urea nitrogen (BUN), creatinine, sodium, potassium and calcium levels.

5. Discussion

In this study, we evaluated the therapeutic effects of sevelamer in patients with DN stage 2-4 and observed that sevelamer significantly reduced HbA_{1c} and postprandial blood sugar.

Similar to our findings, Vlassara et al (5) found that treatment with sevelamer can reduce HbA_{1c} levels.

Table 1. HbA_{1c} levels and lipid profile before and after study

	Before the study	3 Months later	<i>P</i> value
HbA _{1c} (%)	7.92 \pm 1.41	6.99 \pm 1.96	0.001
Triglyceride (mg/ dL)	184.89 \pm 80.77	177.44 \pm 80.40	0.54
Cholesterol (mg/ dL)	178.78 \pm 44.49	168.39 \pm 41.76	0.2
HDL-C (mg/ dL)	48.17 \pm 7.68	47.89 \pm 7.44	0.7
LDL-C (mg/dL)	94.61 \pm 40.57	85.56 \pm 30.71	0.32

Table 2. Electrolytes, CBC and hs-CRP changes during the study

	At baseline	1st month	2nd month	3rd month	P value
Hemoglobin (g/dL)	12.06±1.11	12.04±1.00	12.05±0.89	12.04±1.45	0.93
WBC (/mm ³)	7820.56±2072.47	8369.44±1923.01	8322.22±1852.68	8380.00±2316.42	0.29
Platelet (×10 ⁶)/ mm ³	232.44±74.40	234.41±75.69	219.55±67.15	223.33±72.63	0.29
FBS (mg/dL)	154.78±85.99	144.06±82.37	143.67±84.28	135.89±86.70	0.27
Postprandial BS (mg/dL)	236.94±86.12	206.89±76.55	197.28±75.82	191.56±90.64	<0.001
BUN (mg/ dL)	84.22±38.30	77.11±37.00	79.33±42.19	75.56±36.78	0.21
Creatinine (mg/dL)	2.07±0.81	2.04±0.88	1.97±0.83	1.99±0.93	0.6
Na (mEq/L)	139.50±28.9	139.17±3.45	139.17±3.50	139.17±3.97	0.9
K (mEq/L)	4.43±0.67	4.48±0.65	4.43±0.57	4.26±0.66	0.57
Ca (mg/dL)	9.92±0.31	9.71±0.24	9.43±0.57	9.83±0.44	0.55
P (mg/dL)	4.95±0.58	4.92±0.63	4.75±0.77	4.22±0.82	<0.001
hs-CRP (mg/L)	2.61±1.66	2.65±0.92	2.55±0.92	2.56±1.90	0.88

While in another study by Yubero-Serrano and colleagues (11), HbA1c was not significantly reduced in overall population, but had significant changes in female patients. It is suggested a direct association between AGEs and insulin resistance, as by reduction of AGEs, the resistance is decreased and may result in better glucose hemostasis (12). Considering the effects of sevelamer on reducing AGEs, it is possible that sevelamer could improve glucose tolerance and reduce HbA1c, beside its phosphorus reducing effects (5).

Our results indicated that the consumption of sevelamer does not affect lipid profile in DN patients. This finding is partially in line with the findings of the study conducted by Ahmadi et al (13) in which they studied hemodialysis patients and found that sevelamer decreases triglycerides levels but does not affect their LDL-C, HDL-C, and total serum cholesterol. However, our finding regarding the patients' lipid profile was inconsistent with the findings of the studies conducted by Chertow et al (14), Shantouf et al (15) and Burke et al (16). Additionally, in the study of Vlassara et al (5) on DN patients, they found significant lipid lowering effects on triglycerides and total cholesterol, but no changes in HDL-C and LDL-C levels. Sevelamer had no effects on inflammatory marker, hs-CRP, in our study. While previous studies have reported sevelamer could reduce circulating hs-CRP in patients with CKD and on dialysis (10,15-18). The two other studies evaluating the effects of sevelamer in DN patients have also shown significant inflammation lowering and reducing oxidative stress effects for sevelamer (5,11). The differences in proportion of samples in each study and the duration of the treatment could be a cause for these observed differences.

6. Conclusions

In conclusion, the addition of sevelamer to the treatment

of patients with DN resulted in reduction of HbA1c and postprandial blood sugar levels, beside their phosphorus lowering benefits. Sevelamer showed no significant effects on lipid profile and hs-CRP. However, these results must be confirmed by larger and longer duration of therapy trials.

Study limitations

The present study is limited in several aspects. First, the proportion of patients in this study was relatively small, limiting its statistical power. This was a single center nonrandomized with no control group study, hence it has its inherent limitations. We also did not measure AGEs levels in our patients to evaluate sevelamer effects. Also, short duration of the intervention is another limitation of the study.

Authors' contribution

All the authors have contributed towards performing the study and preparation of the manuscript and they all have approved the latest version of the article.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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